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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,224	03/02/2004	Yumi Matsuzaki	US-162	9934

38108 7590 04/16/2007

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/790,224	MATSUZAKI ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007 and 20 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7 and 10-12* is/are pending in the application.

4a) Of the above claim(s) *5-7,10 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/20/07 and 1/5/07 has been entered.

2. Claims 1, 5-7, and 10-12 are pending in the application.

3. Applicant's amendment to the claims, filed on 1/5/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

4. Receipt of a Declaration under 37 CFR 1.132, filed on 2/20/07, is acknowledged.

5. Applicant's arguments filed on 1/5/07 have been fully considered and are deemed to be persuasive to overcome some of the objections and/or rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

6. The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

7. Claims 5-7, 10, and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/13/05.

8. Claims 1 and 11 are being examined on the merits.

Claim Rejections - 35 USC § 112, First Paragraph

9. The written description rejection of claim 1 under 35 U.S.C. § 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. Claim 11 is included in the instant rejection for reasons that follow. Thus, claims 1 and 11 are rejected.

RESPONSE TO ARGUMENT: Applicant argues: 1) the specific mutation of the GS is recited and the sequences of the GS and ArgR polypeptides were known; 2) the claim requires the variant sequences to be at least 90% homologous to the recited sequences; 3) "[s]ufficient information" was known about these sequences to fully describe the genus of variants; and 4) one of skill could determine those variants that fell within the "90% or more homologous" limitation.

Applicant's argument is not found persuasive. Applicant's argument is not found persuasive. The examiner maintains the position that the two disclosed species of the claimed genus fail to represent the wide variation within the genus of claimed modified coryneform bacteria. Claim 1 is drawn to a genus of coryneform bacteria having *any* modification to reduce or eliminate expression of an arginine repressor polypeptide that is at least 90% homologous (homologous is interpreted herein as meaning "identical") to SEQ ID NO:16 and having enhanced GS activity, wherein the GS polypeptide is at least

90% homologous to SEQ ID NO:20. Claim 11 is drawn to a genus of coryneform bacteria having (in relevant part) any modification that results in a disruption in the chromosomal gene encoding the arginine repressor of SEQ ID NO:16. According to a dictionary definition of "disruption," the term has a meaning of "to interrupt the normal course or unity of" (Merriam Webster Online Dictionary at www.m-w.com/, last viewed on 4/11/07). In view of this definition, the claim has been interpreted as meaning that the chromosomal gene has any alteration, which is not limited to decreasing or eliminating expression of the gene, such that the gene no longer encodes SEQ ID NO:16. Put another way, the claim has been broadly interpreted in accordance with MPEP 2111.01 as encompassing any alteration to the gene encoding SEQ ID NO:16 such that the gene no longer encodes SEQ ID NO:16, including alterations that result in the gene encoding any other protein having any function.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a

sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only two species of the claimed genus of coryneform bacteria, *i.e.,* strain 2256ΔargRΔglnE, also referred to as strain FERM BP-08630 and strain 2256ΔargRAde, also referred to as FERM BP-08631. Other than these two representative species, the specification fails to disclose any additional species of the claimed genus of coryneform bacteria, which, because of the allowed structural variation of the ArgR and GS sequences, encompasses widely variant species, which is undisputed by applicant. The Courts generally accept as fact an examiner's finding that is undisputed by applicant. See *In re Kunzmann*, 140 USPQ 235 (CCPA 1964). Although applicant argues "[s]ufficient information" regarding these sequences was known, it is unclear as to what "information" is being referenced.

Given the lack of description of a representative number of modified coryneform bacteria, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

10. The scope of enablement rejection of claim 1 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. Claim 11 is included in the instant rejection for reasons that follow. Thus, claims 1 and 11 are rejected.

RESPONSE TO ARGUMENT: Applicant argues: 1) the specific mutation of the GS is recited and the sequences of the GS and ArgR polypeptides were known; 2) the

claim requires the variant sequences to be at least 90% homologous to the recited sequences; 3) "[s]ufficient information" was known about these sequences to fully enable the genus of variants; 4) one of skill could determine those variants that fell within the "90% or more homologous" limitation; and 5) in view of the specification and state of the art, only routine experimentation is required to make the full scope of the claimed invention.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to enable the full scope of claimed coryneform bacteria. Claim 1 is so broad as to encompass all coryneform bacteria having *any* modification to reduce or eliminate expression of an arginine repressor polypeptide that is at least 90% homologous (homologous is interpreted herein as meaning "identical") to SEQ ID NO:16 and having enhanced GS activity, wherein the GS polypeptide is at least 90% homologous to SEQ ID NO:20. As noted above, claim 11 is so broad as to encompass a coryneform bacterium having any alteration to the gene encoding SEQ ID NO:16, including alterations that result in the gene encoding any other protein having any function. In this case, the specification discloses only two modifications that result in enhanced glutamine synthetase activity as encompassed by the claim, *i.e.,* overexpression of GS and mutation of the adenylation site of the glutamine synthetase of SEQ ID NO:20 at position 405. The specification discloses only a single modification to an arginine repressor, *i.e.,* knockout of the *argR* gene of SEQ ID NO:15 by homologous recombination. The specification discloses only two working examples of coryneform bacteria comprising these modifications, *i.e.,* strain 2256ΔargRΔglnE, also

referred to as strain FERM BP-08630 and strain 2256ΔargRAde, also referred to as FERM BP-08631. Other than these working examples, the specification fails to provide any additional *specific* guidance for modifying a coryneform bacterium with an expectation of obtaining a bacterium having the desired activity/utility. The effects of modifying a bacteria, particularly modifications to nucleic acids encoding L-amino acid biosynthetic pathway enzymes and regulatory proteins thereof with an expectation of the bacteria maintaining the ability to produce a desired L-amino acid, is *highly* unpredictable as evidenced by Rhee et al. (cited in the 8/11/2005 Office action), Branden et al. (cited in the 1/27/2006 Office action) and Witkowski et al. (cited in the 1/27/2006 Office action). Although applicant argues "[s]ufficient information" regarding these sequences was known, it is unclear as to what "information" is being referenced.

In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability, and the amount of non-routine experimentation required, it is the examiner's position that undue experimentation is required for a skilled artisan to make the full scope of claimed bacteria.

Claim Rejections - 35 USC § 103

11. The rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Suga et al. in view of Jakoby et al. and Nakayama et al. is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. Newly added claim 11 is included in the instant rejection. Thus, claims 1 and 11 are rejected herein.

RESPONSE TO ARGUMENT: Applicant argues that the statement of Jakoby et al. that "the central enzyme for the assimilation of ammonia under limiting conditions is glutamine synthase" is not supported by a scientific publication or data. According to applicant, the Figure 1 data of Jakoby et al., while showing that the activity of wild-type GS decreases in the presence of ammonium ions relative to Y405F mutant, in amino acid fermentation, the ammonium ion concentration is generally very low such that GS activity does not decrease. Thus, according to applicant, one of ordinary skill in the art would not take from the reference of Jakoby et al. that it is necessary to enhance GS activity to produce amino acids.

Applicant's argument is not found persuasive. Although applicant states that Jakoby et al. provides no evidence to support the disclosed statement that "the central enzyme for the assimilation of ammonia under limiting conditions is glutamine synthase," applicant does not appear to disagree with this statement and provides no objective evidence to the contrary. What appears to be at issue is whether one of ordinary skill in the art would have been motivated to make the claimed bacterium. According to applicant, one of ordinary skill in the art would have recognized that the teachings of Jakoby et al., particularly the experimental data, is not relevant to amino acid production as the level of ammonium used in the experiment of Jakoby et al. is allegedly significantly higher than that used in culturing of bacteria for amino acid biosynthesis. However, applicant's argument appears to be mere speculation, particularly as there is no evidence of record to support applicant's assertion that the levels of ammonium used by Jakoby et al. are different from that used in fermentation

media for amino acid production. Even assuming *arguendo* such evidence were made of record, it would appear that one of ordinary skill in the art would recognize the teachings of Jakoby et al. as being relevant to the production of amino acids. Assuming that applicant's assertion that "the ammonium concentration is generally very low" in amino acid fermentation were supported by objective evidence, the reference of Jakoby et al. would appear to be relevant as the reference acknowledges that GS is a central enzyme for nitrogen assimilation – not under any levels of ammonium concentration – but "*under limiting conditions*" (emphasis added; p. 305, column 1, bottom). Also, Jakoby et al. acknowledges that *C. glutamicum* is used in the industrial production of amino acids and that "[a] crucial step of amino acid production [by *C. glutamicum*]...is the assimilation of nitrogen" (p. 303, left column, bottom) and further acknowledges that "we are interested in global regulatory mechanisms in *C. glutamicum*." Thus, even assuming *arguendo* the levels of ammonium were higher in the experiments of Jakoby et al. relative to the level used in typical amino acid fermentation, one of ordinary skill in the art would recognize that the teachings of Jakoby et al. are nonetheless relevant to amino acid production using *C. glutamicum*.

Regarding applicant's statement that one would not take from the teachings of the reference of Jakoby et al. that it is necessary to enhance GS activity to produce amino acids, the examiner has not suggested that in view of the reference of Jakoby et al., one of ordinary skill in the art would recognize that "it is *necessary* to enhance GS activity to produce amino acids" (emphasis added). Instead, in view of the teachings of Jakoby et al., one of ordinary skill in the art would recognize that GS is "the central

enzyme for the assimilation of ammonium" (p. 305, column 1, bottom) and that the activity of wild-type glutamine synthetase is significantly reduced in the presence of ammonium, while the activity of the Y405F mutant is not downregulated in the presence of ammonium (p. 306, left column, top).

Applicant further argues the Declaration under 37 CFR 1.132 demonstrates non-obviousness by showing GS activity in L-glutamine producing strains is "very low" and enhancing GS activity is not a critical factor in amino acid fermentation.

Applicant's argument is not found persuasive. According to the Declaration at item 4, "[t]he data described herein shows that GS activity is very low in L-glutamine-producing strains, and therefore enhancement of GS activity is not a critical factor in amino acid fermentation." Apparently, applicant takes the position that because GS activity is lower than GDH activity in a glutamine-producing strain of bacterium, this is evidence that the enzyme is not critical for amino acid production. However, it is unclear to the examiner as to how, by comparing measurement of GS and GDH activities in a wild-type or sulfaguanine resistant strain, applicant arrives at the conclusion that "[t]he data described herein shows that GS activity is very low in L-glutamine-producing strains, and therefore enhancement of GS activity is not a critical factor in amino acid fermentation." According to MPEP 716.02(b), "'[a]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness.'" In this case, applicant fails to sufficiently explain how the data supports applicant's assertion of non-obviousness as noted above. Applicant is requested to adequately explain the data in accordance with MPEP 716.02(b).

Applicant argues that an ordinarily skilled artisan would not expect the combination of enhancing GS activity and disrupting the arginine repressor would result in the production of L-lysine and L-arginine.

Applicant's argument is not found persuasive. In this case, applicant provides no rationale or line of reasoning in support of the assertion that the combination of references fails to provide a reasonable expectation of success. In the absence of such a rationale or line of reasoning, the examiner maintains the position that the combination of references provides a reasonable expectation of success for making the claimed invention for the reasons of record.

Conclusion

12. Status of the claims:

Claims 1, 5-7, and 10-12 are pending.

Claims 5-7, 10, and 12 are withdrawn from consideration.

Claims 1 and 11 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656